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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/016,737	01/30/98	MURPHY G	8511-007

020583
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HM12/1003

EXAMINER	
DAVIS,M	

ART UNIT	PAPER NUMBER
1642	19

DATE MAILED: 10/03/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/016,737	Murphy et al
Examiner	**Art Unit**
MINH TAM DAVIS	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jul 24, 2001* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above, claim(s) *1-22, 25, and 27* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *23, 24, 26, and 28-37* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Effective February 7, 1998, the Group Art Unit location has been changed, and the examiner of the application has been changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Minh-Tam Davis, Group Art Unit 1642.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 07/24/01 has been entered.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant amends claims 23 and 28 and adds new claims 31-37, which are related to claims 23-24, 26 and 28-30 and are not new matters.

Accordingly, claims 23-24, 26, 28-37 are examined.

The following are the remaining rejections.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, NEW MATTER, NEW REJECTION

Claims 23-24, 26, 28-37 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 23-24, 26, 28-37 are drawn to dendritic cells competent and "enabled" to activate T cells specific for a prostate antigen.

The specification discloses dendritic cells competent and "able" to activate T cells specific for a prostate antigen (p.10, second paragraph). The specification does not disclose nor contemplate dendritic cells competent and "enabled" to activate T cells specific for a prostate antigen.

REJECTION UNDER 35 USC 112, SECOND PARAGRAPH, NEW REJECTION

1. Claims 23, 24, 26, 28-37 are indefinite for the use of the amended language "T cells to a prostate antigen" in claim 23. It is not clear what "T cells to a prostate antigen" are. This rejection could be obviated by amending the claims to replace "T cells to a prostate antigen" with "T cells specific to a prostate antigen".

2. Claims 23, 24, 26, 28-37 are indefinite. It is not clear in claims 23 and 31 how one could distinguish the dendritic cells isolated from the claimed method and those "directly" isolated from peripheral blood, because the claimed dendritic cells seem to be taken directly from peripheral blood for centrifugation. Further, the claims are confusing because it is not clear what

amount of peripheral blood is used for isolating the claimed dendritic cells, versus the amount of perpheral blood for "directly" isolating dendritic cells .

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE, NEW REJECTION

Claims 23, 24, 26, 28-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for human dendritic cells competent and able to activate T cells specific for a protate antigen, wherein the prostate antigen is a lysate of primary prostate tumor cells from a prostate cancer patient, does not reasonably provide enablement for human dendritic cells competent and able to activate T cells specific for a prostate antigen, wherein the prostate antigen is a lysate of LNCaP cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 23, 24, 26, 28-37 are drawn to human dendritic cells competent and able to activate T cells specific for a prostate antigen, wherein the prostate antigen is a lysate of LNCaP cells.

It is of little practical use for human dendritic cells competent and able to activate T cells specific for a protate antigen, wherein the prostate antigen is a lysate of LNCaP cells, because the antigen present on the surface of LNCaP and recognized by T cells could be different and does not exist in primary prostate tumor cells. Characteristics of cultured cell lines generally differ significantly from the characteristics of a primary tumor. Drexler et al (Leukemia and

Lymphoma, 1993, 9:1-25) specifically teach, in the study of Hodgkin and Reed-Sternberg cancer cells in culture, that the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded and that only a few cell lines containing cells that resemble the *in-vivo* cancer cells have been established and even for the *bona fide* cancer cell lines it is difficult to prove that the immortalized cells originated from a specific cancer cell (see attached abstract). Further, Embleton et al (Immunol Ser, 1984, 23:181-207) specifically teaches that in procedures for the diagnosis of osteogenic sarcoma, caution must be used when interpreting results obtained with monoclonal antibodies that had been raised to cultured cell lines and specifically teach that cultured tumor cells may not be antigenically typical of the tumor cell population from which they were derived and it is well established that new artifactural antigens can occur as a result of culture (see attached abstract). Hsu (in Tissue Culture Methods and Applications, Kruse and Patterson, Eds, 1973, Academic Press, NY, see abstract, p.764) specifically teaches that it is well known that cell cultures *in vitro* frequently change their chromosomal constitutions (see abstract). The evidence presented clearly demonstrates that in cell culture systems, in general, and in cancer derived cell lines in particular, that artifactural chromosome constitutions and antigen expression are expected and must be taken into account when interpreting data received from cell line assays. Further, Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish

cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary -type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not, yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interations. Thus, based on the cell culture data presented in the specification, it could not be predicted that primary prostate tumor cells have the same surface antigens as LNCaP cells.

In view of the above, it would have been undue experimentation for one of skill in the art to practice the claimed invention.

REJECTION UNDER 35 USC 102, NEW REJECTION

Claims 23, 24, 31-36 are rejected under 35 U.S.C. 102(e) as being anticipated by Cohen et al (of record), as evidenced by Sallusto et al (of record), Koch et al, 1995, IDS #BS, and Czerniecki et al, 1997, J Immunol, 159: 3823-3827.

Claims 23, 24, 31-36 are drawn to an increased number of human dendritic cells, competent and enabled to activate T cells to a prostate antigen, of at least 20 fold more, as compared to those directly isolated from peripheral blood. The prostate antigen is lysate of prostate tumor cells. The dendritic cells are immature dendritic cells, isolated from normal individual or from a prostate cancer patient. The activated T cells are CD4+ or CD8+.

Cohen et al teach isolation of dendritic cells from peripheral blood from human normal individual and a patient with prostate cancer, by leukaphoresis and centrifugation (columns 5-6, and Examples 1-2). Cohen et al teach that calcium ionophore is used to stimulate monocytes

isolated during the process into dendritic cells (abstract). Cohen et al teach that the enriched dendritic cells are incubated with a prostate tumor lysate, which activates the dendritic cells to present prostate tumor cell antigens. Cohen et al further teach that said dendritic cells after incubated with a prostate tumor lysate, and reintroduced into the patient could reduce the size of prostate tumor (Example 2).Cohen et al teach that certain specific combination of cytokines have been used successfully to amplify or partially substitute for the activation/conversion achieved with calcium ionophore. These cytokines include rhGM-CSF, rhIL-2, reIL-4 and rhIL-12. Each cytokine when given alone is inadequate for optimal upregulation (column 10, lines 54-60). Cohen et al teach that the yield of dendritic cells is 100 fold over previous dendritic cell isolation methods (column 12, first paragraph).

Cohen et al do not teach that the number of dendritic cells are at least 20 fold more, as compared to those directly isolated from peripheral blood. Cohen et al do not teach that the dendritic cells are immature dendritic cells. Cohen et al do not teach that the activated T cells CD4+ or CD8+.

Sallusto, F et al, 1994, J Exp Med, 179: 1109-1118, teach that the exposure to Granulocyte/Macrophage colony-stimulating factor plus interleukin 4 converts blood mononuclear cells to dendritic cells, and that cultured, isolated dendritic cells when maintained by Granulocyte/Macrophage colony-stimulating factor plus interleukin 4 could efficiently present soluble antigen. Since exposure to calcium ionophore gives the same result as to exposure to cytokines, as taught by Cohen et al, one of ordinary skill in the art would have expected that the dendritic cells taught by Cohen et al would inherently process and present antigen, similar to dendritic cells previously exposed to cytokines.

Koch et al teach that mature dendritic cells down regulate their processing capacity, whereas a subset of immature dendritic cells could handle native protein Ag.

Thus as evidenced by Salluto et al, and Koch et al, since the dendritic cells taught by Cohen et al would inherently process and present antigen, they would inherently be immature

dendritic cells. In addition, one of ordinary skill in the art would have expected that the dendritic cells taught by Cohen et al are not mature dendritic cells, because mature dendritic cells down regulate their processing capacity, as taught Koch et al, whereas the dendritic cells taught by Cohen et al could reduce prostate tumor size, an effect due to the injected dendritic cells, as taught by Cohen et al (column 12, example 2).

Czerniecki et al teach that monocytes isolated by leukaphoresis and centrifugation of human peripheral blood, and purified immature dendritic cells, after treated with calcium ionophore, would enhance sensitization of CD4+ and CD8+ T cells (abstract).

Thus as evidenced by Czerniecki et al, one of ordinary skill in the art would have expected that the dendritic cells taught by Cohen et al would inherently activate CD4+ and CD8+ T cells.

Futher, one of ordinary skill in the art would have expected that the yield of dendritic cells taught by Cohen et al would be inherently at least 20 fold more, as compared to those directly isolated from peripheral blood, because Cohen et al teach that the yield of dendritic cells is 100 fold over previous dendritic cell isolation methods.

The reference does not specifically teach that the number of dendritic cells are at least 20 fold more, as compared to those directly isolated from peripheral blood, wherein said dendritic cells are immature dendritic cells, and could activated CD4+ or CD8+ T cells. However, the claimed dendritic cells appears to be the same as the prior art dendritic cells. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

ANSWER TO APPLICANT'S ARGUMENT AGAINST 102 REJECTION

Applicant argues that the dendritic cells by Cohen et al, after treatment with calcium ionophore are activated, i.e. mature, and thus cannot process and present antigen. Applicant again recites the reference by Pinkl which teaches that cells having a membrane antigen phenotype of a dendritic cell without other data can lack the ability to present antigen. Applicant further asserts that on lines 31-36 column 5 of Cohen, the method by Cohen et al converts monocytes to activated dendritic cells. Applicant recites a new reference by Koch et al, which teaches that population of mature dendritic cells are heterogenous, and include small number of immature dendritic cells. Koch et al further teach that mature dendritic cells down regulate their processing capacity, whereas the subset of immature dendritic cells could handle native protein Ag. Applicant asserts that a small population of immature dendritic cells would not be present in the composition of Cohen et al, because Cohen et al describe their dendritic cells as being a homogenous population of activated or mature dendritic cells. Applicant further recites the reference by Czerniecki et al, 1997, co-authored by Cohen and several inventors in the cited reference by Cohen et al, which teaches the activation of dendritic cells by calcium ionophore, and still studies the ability of MOMC treated with calcium ionophore to sensistize autologous T cells *in vitro*. Further, Applicant argues that as newly amended, the instant invention is patentably distinct from Cohen et al.

Applicant's arguments set forth in paper No.14 have been considered but are not deemed to be persuasive for the following reasons:

The recitiation of Pinkl, Koch et al, and Czerniecki et al is acknowledged. It seems that Applicant misinterpretes the word "activated" dendritic cells used by Cohen et al as "mature" dendritic cells. Cohen et al teach that certain specific combination of cytokines have been used successfully to amplify or partially substitute for the activation/conversion achieved with calcium ionophore. These cytokines include rhGM-CSF, rhIL-2, reIL-4 and rhIL-12. Each cytokine when given alone is inadequate for optimal upregulation (column 10, lines 54-60). Sallusto, F et al,

1994, J Exp Med, 179: 1109-1118, teach that the exposure to Granulocyte/Macrophage colony-stimulating factor plus interleukin 4 converts blood mononuclear cells to dendritic cells, and that cultured, isolated dendritic cells when maintained by Granulocyte/Macrophage colony-stimulating factor plus interleukin 4 could efficiently present soluble antigen. Thus it seems that Cohen et al use the language "activation" the same as "conversion", and that exposure to calcium ionophore gives the same result as to exposure to cytokines. As evidenced by Salluto et al, one of ordinary skill in the art would have expected that the dendritic cells taught by Cohen et al would process and present antigen, similar to dendritic cells previously exposed to cytokines. Further, as recited in previous Office action, in example 2 of Cohen et al, the dendritic cells have been successfully used for reducing prostate tumor size (column 12, lines 27-32). Thus one of ordinary skill in the art would have expected that the dendritic cells taught by Cohen et al are fully functional, i.e. processing and presenting antigen, and activating specific T cells which are expected to responsible for reducing tumor growth. Further, Applicant is arguing limitations not recited in the claims as presently constituted, since the submitted amendment has not been and will not be entered.

REJECTION UNDER 35 USC 103

1. Rejection under 35 USC 103 of claim 26 pertaining to obviousness over Cohen et al in view of Lutz et al remains for reasons already of record in paper No.11.

Applicant argues that as newly amended, the instant invention is patentably distinct from the dendritic cells of Cohen et al for the reasons set forth above. Further, Applicant argues that the dendritic cells taught by Cohen et al do not process and present antigen. Thus the reference by Lutz et al adds nothing to render the claim obvious.

Applicant's arguments set forth in paper No.14 have been considered but are not deemed to be persuasive for the following reasons:

The claimed dendritic cells are not patentably distinct from the dendritic cells of Cohen et al for the reasons set forth above. Further, one of ordinary skill in the art would have expected that the dendritic cells taught by Cohen et al process and present antigen.

2. Rejection under 35 USC 103 of claims 28, 29 pertaining to obviousness over Cohen et al in view of Taylor et al remains for reasons already of record in paper No.11.

Applicant argues that as newly amended, the instant invention is patentably distinct from the dendritic cells of Cohen et al for the reasons set forth above. Further, Applicant argues that the dendritic cells taught by Cohen et al do not process and present antigen. Thus one cannot combine the two references.

Applicant's arguments set forth in paper No.14 have been considered but are not deemed to be persuasive for the following reasons:

The claimed dendritic cells are not patentably distinct from the dendritic cells of Cohen et al for the reasons set forth above. Further, one of ordinary skill in the art would have expected that the dendritic cells taught by Cohen et al process and present antigen.

3. Rejection under 35 USC 103 of claim 30 pertaining to obviousness over Cohen et al in view of Taylor et al, further in view of Lutz et al remains for reasons already of record in paper No.11.

Applicant argues that as newly amended, the instant invention is patentably distinct from the dendritic cells of Cohen et al for the reasons set forth above. Further, Applicant argues that the dendritic cells taught by Cohen et al do not process and present antigen. Thus none of the added references suggest or disclose the claimed invention.

Applicant's arguments set forth in paper No.14 have been considered but are not deemed to be persuasive for the following reasons:

The claimed dendritic cells are not patentably distinct from the dendritic cells of Cohen et al for the reasons set forth above. Further, one of ordinary skill in the art would have expected that the dendritic cells taught by Cohen et al process and present antigen.

REJECTION UNDER 35 USC 103, NEW REJECTION

Claim 37 is rejected under 35 U.S.C. 103(a) as being unpatentable over Cohen et al, in view of Stites et al, eds, Basic and Clinical Immunology, 1991,Appleton & Lange, CA p.45.

Claim 37 is drawn to dendritic cells which are HLA-matched for a recipient.

The teaching of Cohen et al has been set forth. Cohen et al however do not teach that dendritic cells isolated from normal individuals are HLA-matched for a recipient.

Stites et al teach T cells only recognize immunogens in conjuction with MHC, which is well known in the art to be a synonym for HLA molecule (p.45). Stites et al teach that matching of these HLA antigen is important in organ transplantation.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to match HLA of dendritic cells from normal individual for a recipient, because Stites et al teach T cells only recognize immunogens in conjunction MHC, which is well known in the art to be a synonym for HLA molecule, and because one of ordinary skill in the art would have expected that T cells specific for prostate tumor antigen would not be activated by allogenic dendritic cells presenting a prostate tumor antigen bound to a different HLA type. Further, one of ordinary skill in the art would have expectd that the injected dendritic cells with a different HLA type than the recipient would be rejected due to histoincompatibility, as taught by Stites et al. One of ordinary skill in the art would have motivated to match HLA of the dendritic cells for a recipient with a reasonable expectation of success.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Minh-Tam B. Davis whose telephone number is (703) 305-2008. The examiner can normally be reached on Monday-Friday from 9:30am to 3:30pm, except on Wesnesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Tony Caputa, can be reached on (703) 308-3995. The fax phone number for this Group is (703) 308-4227.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0916.

Minh-Tam B. Davis
September 20, 2001

SUSAN UNGAR, PH.D
PRIMARY EXAMINER